Prospective Study of Fruit and Vegetable Consumption and Incidence of Colon and Rectal Cancers

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Background: **Frequent consumption of fruit and vegetables has been associated with a reduced risk of colorectal cancer in many observational studies.** ***Methods:*** **We prospectively investigated the association between fruit and vegetable consumption and the incidence of colon and rectal cancers in two large cohorts: the Nurses' Health Study (88 764 women) and the Health Professionals' Follow-up Study (47 325 men). Diet was assessed and cumulatively updated in 1980, 1984, 1986, and 1990 among women and in 1986 and 1990 among men. The incidence of cancer of the colon and rectum was ascertained up to June or January of 1996, respectively. Relative risk (RR) estimates were calculated with the use of pooled logistic regression models accounting for various potential confounders. All statistical tests were two-sided.** ***Results:*** **With a follow-up including 1 743 645 person-years and 937 cases of colon cancer, we found little association of colon cancer incidence with fruit and vegetable consumption. For women and men combined, a difference in fruit and vegetable consumption of one additional serving per day was associated with a covariate-adjusted RR of 1.02 (95% confidence interval [CI] = 0.98–1.05). A difference in vegetable consumption of one additional serving per day was associated with an RR of 1.03 (95% CI = 0.97–1.09). Similar results were obtained for women and men considered separately. A difference in fruit consumption of one additional serving per day was associated with a covariate-adjusted RR for colon cancer of 0.96 (95% CI = 0.89–1.03) among women and 1.08 (95% CI = 1.00–1.16) among men. For rectal cancer (total, 244 cases), a difference in fruit and vegetable consumption of one additional serving per day was associated with an RR of 1.02 (95% CI = 0.95–1.09) in men and women combined. None of these associations was modified by vitamin supplement use or smoking habits.** ***Conclusions:*** **Although fruits and vegetables may confer protection against some chronic diseases, their frequent consumption does not appear to confer protection from colon or rectal cancer. [J Natl Cancer Inst 2000;92:1740–52]**

About two decades ago, Doll and Peto *(1)* suggested that up to 90% of U.S. deaths from cancer of the large bowel might be avoidable through alterations in diet. Alcohol intake *(2)* and red meat consumption *(3)* may increase the risk of colorectal cancer, and the use of multivitamin supplements appears to decrease the risk *(2,4)*. Consumption of fruit and vegetables could confer protection through anticarcinogenic components, such as antioxidants (in particular, carotenoids and vitamin C), folic acid, flavonoids, organosulfides, isothiocyanates, and protease inhibitors that might influence DNA damage and thus reduce mutations *(5)*. Furthermore, these foods provide fermentable fiber, which decreases transit time, lowers pH, and produces potentially anticarcinogenic short-chain fatty acids *(6)*. Indeed, many epidemiologic studies [reviewed in *(6)*]—mostly retrospective—have reported some protective association between fruit and vegetable consumption and colorectal cancer risk. In case–control studies, however, diet is assessed retrospectively; hence, such studies are prone to recall or reporting bias because case patients and control subjects are likely to differ in their reporting of their dietary habits.

We have shown previously that fiber intake was unrelated to risk of colorectal cancer *(7)* in two large prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals' Follow-up Study (HPFS), whereas long-term multivitamin supplement use was inversely associated with risk *(4)*. We now examine prospectively overall consumption of fruit and vegetables and consumption of certain subgroups of fruits and vegetables in relation to the incidence of colon and rectal cancers among women and men.

Subjects and Methods

Study Cohorts

The NHS was initiated in 1976, when 121 700 female registered nurses aged 30–55 years completed a self-administered questionnaire providing information on demographics, lifestyle, and medical history. Similarly, the HPFS consisted of 51 529 male health professionals, including dentists, veterinarians, pharmacists, optometrists, osteopaths, and podiatrists who were 40–75 years of age at enrollment in 1986. The NHS was approved by the Institutional Review Board (IRB) of the Brigham and Women's Hospital, Boston, MA, and the HPFS received IRB approval from the Harvard School of Public Health, Boston. Participants in both cohorts have been followed through self-administered biennial questionnaires that serve to update information on lifestyle factors and disease.

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See "Notes" following "References."

The study populations for the present analyses consisted of all women free of cancer in 1980 who completed the 1980 food-frequency questionnaire (FFQ) and who reported a total caloric intake between 500 and 3500 calories per day (88 764 women) as well as all men free of cancer in 1986 who completed the 1986 FFQ and who reported a total caloric intake between 800 and 4200 calories per day (47 325 men). A higher proportion of HPFS participants than of NHS participants completed the diet questionnaire, since the diet questions were part of the enrollment questionnaire for HPFS, whereas diet was first assessed 4 years after study initiation in the NHS.

Ascertainment of Cases

On each biennial questionnaire, we ask cohort participants whether cancer of the colon or rectum has been diagnosed during the previous 2 years. Deaths are reported to us primarily through family members; to identify fatalities among nonresponders, we use the National Death Index. We also receive verification of deaths from the U.S. Postal Service. We estimate that more than 98% of deaths are ascertained *(8)*.

When a participant (or next of kin for decedents) reports a diagnosis of cancer, we seek permission to obtain relevant medical records and pathology reports. A study physician blinded to all questionnaire data reviews the medical records to extract information on the histologic type, the anatomic location, and the stage of the cancer. Only cases of invasive adenocarcinoma were included in this analysis. Cases of carcinomas *in situ* were not considered because only a relatively small proportion of *in situ* cancers becomes invasive and, thus, the risk factor profile for the two types of cancer may differ.

Dietary Assessment

Data on dietary intake were collected repeatedly in both cohorts by validated self-administered semiquantitative FFQs *(9,10)*. In the NHS, diet was assessed in 1980, 1984, 1986, and 1990; in the HPFS, diet was assessed in 1986 and 1990.

In 1980, the FFQ used for the NHS consisted of 61 food items, including six fruits and 11 vegetables. The 1984 FFQ was expanded to include 15 fruits and 28 vegetables; the questionnaires used in 1986 and 1990 were similar to the questionnaire used in 1984. In the HPFS, the 1986 and 1990 FFQs were similar to the expanded NHS questionnaires. Nine mutually exclusive response possibilities were provided for the frequency of intake in both cohorts. The choices ranged from "almost never or less than once per month" to "six or more times per day." Participants reported their average intake of a prespecified portion size for each food over the previous year. The reproducibility and validity of the FFQ for both women and men have been reported previously *(9,11)*. Responses regarding individual food items were converted to average daily intake of each fruit and vegetable item for each participant. We combined the average daily intake figures for individual food items to compute total fruit and vegetable intake as well as intake of composite fruit and vegetable groups. Fruit and vegetable subgroups were defined *a priori* on the basis of criteria used by Smith et al. *(12)*; the groups were modified to conform to our questionnaires *(13)*. The composite items are described in Appendix Tables 1 and 2. We did not include potatoes as part of the vegetable category, but we did classify sweet potatoes as a vegetable. We also examined the consumption of individual fruits and vegetables in relation to colon and rectal cancer incidence.

Validity on the basis of individual food items has been documented by comparisons with multiple weighted dietary records, correcting for within-person weekly variation in diet *(14,15)*. In the NHS, the average correlation coefficient comparing responses for specific fruits and vegetables on the 1980 FFQ with intake from four 1-week dietary records corrected for within-person variation was about .54, ranging from .17 for spinach to .84 for orange juice *(14)*. In the HPFS, correlations between intakes reported on the FFQ and those reported in dietary records, corrected for within-person weekly variation in diet, were, on average, .57 for specific fruits and vegetables, ranging from .25 for kale, mustard, or chard greens to .95 for bananas *(15)*. Using the same dietary assessment methods, we found that high intake of fruit and vegetables predicted lower risk of ischemic stroke *(13)* and of myocardial infarction (Joshipura KJ: personal communication); thus strong evidence exists for an important variation in fruit and vegetable intake within these cohorts and that this variation is measurable.

Statistical Analysis

Consumption of fruit and of vegetables was grouped in five categories: fewer than 1.5 servings/day (denoted as 1 serving/day or fewer [referent category]), 1.5–2.4 servings/day (2 servings/day), 2.5–3.4 servings/day (3 servings/day), 3.5–4.4 servings/day (4 servings/day), and 4.5 or more servings/day (⩾5 servings/day). Few participants consumed fewer than 1 serving of fruit and vegetables combined; thus, the categories for combined fruit and vegetable consumption were as follows: fewer than 2.5 servings/day (2 servings/day or fewer [referent category]), 2.5–3.4 servings/day (3 servings/day), 3.5–4.4 servings/day (4 servings/day), 4.5–5.4 servings/day (5 servings/day), and 5.5 or more servings/day (⩾6 servings/day). For composite fruit and vegetable groups, cut points of the categories had to be chosen differently because of the lower frequency of intake. Daily consumption of fruit and vegetables was calculated from the frequencies prespecified on the FFQ; relative risk (RR) estimates for 1 additional serving per day were obtained with the use of daily consumption as a continuous variable. To avoid undue influence of outliers, we truncated intake at 10 servings/day for fruit groups and vegetable groups (i.e., self-reported consumption of >10 servings/day was coded as 10 servings/day) and at 15 servings for the combined fruit and vegetable intake. Only less than 0.5% of participants reported consumption of more than 10 servings of fruit or vegetables a day.

Analyses were carried out separately for colon and rectal cancers. We calculated incidence rates for each category of fruit and vegetable intake by dividing the number of new cases of colon or rectal cancer by person-years of follow-up. We calculated person-years of follow-up for each participant from the date of return of the 1980 questionnaire (NHS) or the 1986 questionnaire (HPFS) to the date of diagnosis of colon or rectal cancer, death, or the end of follow-up (with a cutoff date of June 1, 1996, for the NHS and January 31, 1996, for the HPFS), whichever occurred first. Participants who reported having Crohn's disease, ulcerative colitis, or cancers other than nonmelanoma skin cancer were excluded at baseline, and follow-up was censored when these diseases were diagnosed after baseline.

Pooled logistic regression analysis *(16)* with 2-year follow-up intervals was used to calculate RR estimates and 95% confidence intervals (CIs) adjusted for established or suspected colorectal cancer risk factors. Pooled logistic regression analysis is asymptotically equivalent to the Cox regression model with time-dependent covariates, given short time intervals and low probability of the outcome within the intervals *(16,17)*. All statistical tests were two-sided. Analyses were adjusted for age (5-year categories), family history of colorectal cancer, prior sigmoidoscopy (prior to 1990 among women and prior to 1988 among men), height (continuous), body mass index (BMI = weight/height^2) (continuous), physical activity (in METS [metabolic equivalents, i.e., working metabolic rate/resting metabolic rate]/week), regular aspirin use (women: never or <1 tablet/week, 1–6 tablets/week, or ⩾7 tablets/week; men: <2 times/week or ⩾2 times/week), pack-years of smoking (women: 35 years or more in the past; men: before age 30 years), vitamin supplement use (ever use of multivitamins or vitamins A, C, or E), alcohol consumption (none, <10 g/day, 10–19.9 g/day, 20–29.9 g/day, or ⩾30 g/day), total caloric intake (continuous), red meat consumption (<1 serving/week, 1 serving/week, 2–4 servings/week, 5–6 servings/week, or ⩾1 servings/day), and (among women) menopausal status and postmenopausal hormone use (never, current, or past). All covariates were repeatedly assessed and updated in the analysis. Vitamin use was defined as ever use of any vitamin. In 1986, 42% of men reported current use and another 19% reported past use of multivitamins; in 1990, 39% of men reported currently using multivitamins.

Total caloric intake was included in the covariate-adjusted model to control for confounding by total energy intake and to minimize extraneous variation due to general underreporting or overreporting of food items on the FFQ *(10)*. To represent long-term dietary patterns of individual subjects as accurately as possible and to reduce within-person variation, we modeled the incidence of colorectal cancer in relation to the cumulative average fruit and vegetable consumption from all available dietary questionnaires up to the end of each 2-year follow-up interval *(18)*. Among women, dietary data from the 1980 questionnaire were used to predict colorectal cancers diagnosed between June 1980 and June 1984; the average of the 1980 and 1984 dietary intake was used to predict outcomes between June 1984 and June 1986; the average of the 1980, 1984, and 1986 FFQs was used to predict colorectal cancer between June 1986 and June 1990; and the average of the 1980, 1984, 1986, and 1990 FFQs was used to predict colorectal cancers from June 1990 to June 1996. Among men, dietary data from the 1986 questionnaire were used to predict the outcomes between January 1986 and January 1990, and the average of 1986 and 1990 dietary intake was used to predict outcomes between January 1990 and January 1996.

Because of the difference in sex, follow-up time, FFQs, and covariates in the two cohorts, analyses were performed separately for each cohort, and the results were later combined with the use of a fixed-effects model weighting the two RR estimates by the inverse of the standard error *(19).* Tests of heterogeneity were used to evaluate whether associations differed between women and men; results are shown separately whenever statistically significant heterogeneity was seen.

Because their vitamin content could possibly contribute to any observed protective effect of fruit and vegetable intake, associations of consumption of fruit and vegetables with colorectal cancer incidence were evaluated separately among vitamin supplement users and nonusers. We also performed separate analyses for ever smokers and never smokers among those participants for whom information on smoking was available.

RESULTS

Table 1 shows the distribution of the baseline standard risk factors for colorectal cancer by frequency of baseline fruit and vegetable consumption in the NHS and HPFS cohorts, respectively. Persons who consumed more fruits and vegetables were generally somewhat older, had a higher prevalence of health-seeking behaviors as indicated by lower rates of smoking, used more vitamin supplements, and had higher rates of physical activity. Participants reporting high consumption of fruit and vegetables also reported a higher mean caloric intake. Higher fruit consumption was accompanied by lower consumption of meat, whereas the association between vegetable and meat intake was less clear.

During 1 327 029 person-years of follow-up, 569 newly diagnosed cases of colon cancer and 155 incident cases of rectal cancer were reported from participants in the NHS. Among the men participating in the HPFS, 368 incident diagnoses of colon cancer and 89 new cases of rectal cancer occurred during the 416 616 person-years of follow-up. Thus, analyses included 937 cases of colon cancer and 244 cases of rectal cancer in the combined cohorts during 1 743 645 person-years of follow-up. No important overall association between fruit and vegetable consumption and colon or rectal cancer incidence was found (Fig. 1). Compared with women who reported 2 or fewer servings of fruit and vegetables per day, the age-adjusted RR of colon cancer was 0.97 (95% CI = 0.69–1.37) for 3 servings/day, 0.90 (95% CI = 0.64–1.25) for 4 servings/day, 1.11 (95% CI = 0.80–1.53) for 5 servings/day, and 1.02 (95% CI = 0.76–1.38) for 6 or more servings/day. The respective values among men were 1.16 (95% CI = 0.85–1.58), 1.09 (95% CI = 0.79–1.50), 0.89 (95% CI = 0.62–1.29), and 0.95 (95% CI = 0.68–1.31). A

Table 1. Age-standardized risk factors for colorectal cancer, by frequency of fruit and vegetable intake among participants of the Nurses' Health Study in 1980 and participants of the Health Professionals' Follow-up Study in 1986

	Fruit consumption by No. of servings/day*					Vegetable consumption by No. of servings/day*				
	⩽1	2	3	4	⩾5	⩽1	2	3	4	⩾5
					Women					
No. of women	17 463	16 384	27 070	24 122	3725	13 224	23 828	29 852	19 799	2061
Age, y†	46.6	46.6	46.7	46.7	46.8	46.7	46.7	46.7	46.7	46.8
Height, cm†	164	164	164	164	164	164	164	164	164	164
Body mass index, kg/m^2†	24.3	24.4	24.4	24.5	24.4	24.3	24.3	24.4	24.6	24.5
Family history of colorectal cancer, % (mother, father, or siblings)	13.0	13.0	12.8	13.5	13.0	12.3	13.1	13.4	12.8	14.8
Prior sigmoidoscopy, %	9.3	9.8	10.3	9.9	10.3	9.6	9.7	9.9	10.2	10.4
Pack-years of smoking >35 y or more in the past†	0.21	0.17	0.16	0.15	0.17	0.16	0.15	0.16	0.17	0.19
Alcohol consumption, g/day†	8.0	7.4	5.8	5.4	5.0	5.9	6.1	6.5	6.7	7.2
Regular physical activity, %‡	34.6	41.1	47.3	52.8	55.6	37.4	42.5	46.0	52.6	56.4
Premenopausal, %	60.5	61.1	61.1	60.4	59.2	60.0	61.1	61.0	60.5	58.8
Current postmenopausal hormone use, %	7.7	8.0	7.8	8.2	8.5	8.4	7.7	7.8	7.9	8.5
Regular aspirin use, ⩾1 time/wk, %	40.3	41.1	41.2	39.6	38.0	39.5	40.7	41.1	40.2	38.3
Vitamin supplement use, %§	34.3	38.8	42.9	46.6	49.3	38.1	40.1	41.7	45.5	47.8
Total caloric intake†	1393	1450	1547	1723	2036	1334	1472	1594	1753	1947
Red meat consumption, ⩾1 serving/day, %¶	21.1	18.9	18.2	19.1	19.7	14.9	16.2	20.3	23.4	24.4
					Men					
No. of men	15 203	14 098	9256	4464	4304	30 466	11 618	3677	1059	505
Age, y†	54.3	54.4	54.5	54.5	54.5	54.4	54.4	54.4	54.4	54.5
Height, cm†	178	178	178	178	178	178	178	178	178	178
Body mass index, kg/m^2†	25.7	25.5	25.4	25.2	25.2	25.5	25.5	25.6	25.6	25.2
Family history of colorectal cancer, % (mother or father)	7.1	7.6	7.8	8.5	8.0	7.5	8.0	7.8	6.3	6.3
Prior sigmoidoscopy, %	15.6	17.4	18.8	18.4	19.3	17.4	17.8	16.8	17.9	19.7
Pack-years of smoking before age 30 y†	6.3	5.3	4.7	4.3	4.5	5.5	5.1	4.9	4.8	4.8
Alcohol consumption, g/day†	13.7	11.5	10.1	8.8	8.2	11.9	10.6	10.0	9.6	8.5
Physical activity, METS/wk†, ‖	15.5	19.8	22.5	24.8	29.8	18.8	21.7	24.5	25.1	28.8
Regular aspirin use, ⩾2 times/wk, %	29.3	29.1	29.9	29.8	28.5	29.5	29.2	29.6	28.6	27.9
Vitamin supplement use, %§	67.7	71.7	74.5	75.2	77.0	70.7	72.9	75.2	74.0	76.6
Total caloric intake†	1778	1939	2089	2205	2439	1848	2155	2349	2506	2601
Red meat consumption, ⩾1 serving/day, %¶	13.6	11.3	10.8	9.4	8.9	10.3	13.4	15.7	14.7	13.5

*Numbers of servings represent average intake of intervals (<1.5, 1.5–2.4, 2.5–3.4, 3.5–4.4, and ⩾4.5 servings/day).

†Mean value.

‡Regular physical activity was defined as engaging in a regular activity at least once a week long enough to work up a sweat.

§Ever use of any vitamin supplement.

¶Red meat consumption was calculated as grams of intake with 140 g = 1 serving.

‖METS = metabolic equivalents, i.e., working metabolic rate/resting metabolic rate. Participants were asked to indicate the physical activities that they performed and how often. Each activity was assigned an METS unit; e.g., jogging = 7, and squash = 12. From this total, METS per week were calculated.

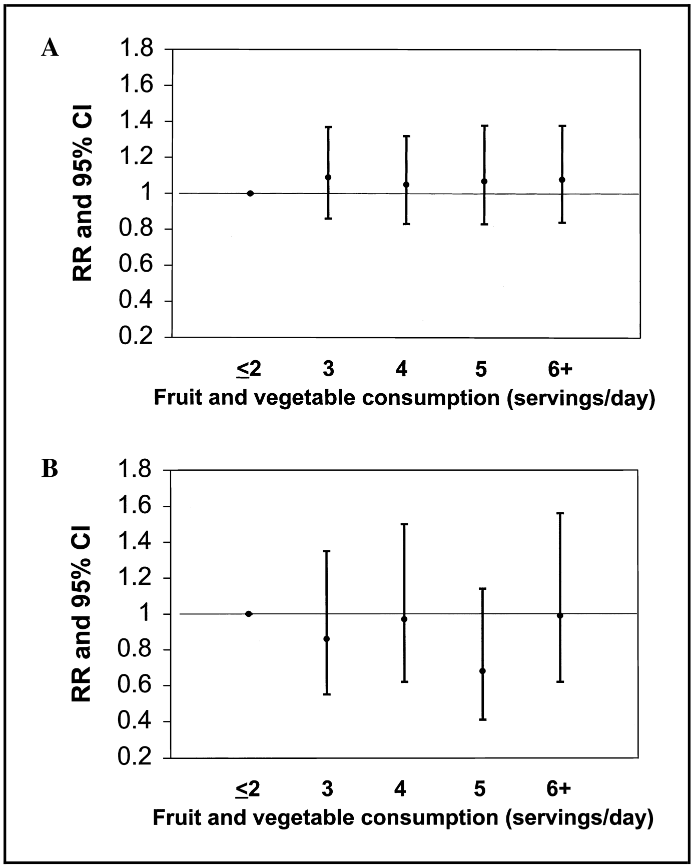

Fig. 1. A) Fruit and vegetable consumption and relative risk (RR) of colon cancer. Covariate-adjusted RR and 95% confidence interval (CI) of colon cancer among women and men according to consumption of fruit and vegetables. Servings represent average intake in each category: ≤2 = <2.5, 3 = 2.5–3.4, 4 = 3.5–4.4, 5 = 4.5–5.4, and 6+ = ≥5.5. RR and 95% CI estimates were adjusted for age, family history of colorectal cancer, sigmoidoscopy, height, body mass index, pack-years of smoking, alcohol intake, physical activity, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption among women and men and additionally among women for menopausal status and postmenopausal hormone use. **B**) Fruit and vegetable consumption and RR of rectal cancer. Covariate-adjusted RRs and 95% CIs of rectal cancer among women and men according to consumption of fruits and vegetables. Servings represent average intake in each category: ≤2 = <2.5, 3 = 2.5–3.4, 4 = 3.5–4.4, 5 = 4.5–5.4, and 6+ = ≥5.5. RR and 95% CI estimates were adjusted for age, family history of colorectal cancer, sigmoidoscopy, height, body mass index, pack-years of smoking, alcohol intake, physical activity, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption among women and men and additionally among women for menopausal status and postmenopausal hormone use.

difference in fruit and vegetable consumption of 1 additional serving/day was associated with an age-adjusted RR of colon cancer of 1.01 (95% CI = 0.98–1.05) among women and 0.99 (95% CI = 0.94–1.04) among men. Additional adjustments for energy and/or for a family history of colorectal cancer, sigmoidoscopy, height, BMI, smoking, alcohol intake, physical activity, aspirin use, use of vitamin supplements, caloric intake, red meat consumption, and menopausal status and postmenopausal hormone use among women only slightly changed the estimates and did not alter interpretation of the results. The covariate-adjusted RR of colon cancer for a difference in fruit and vegetable consumption of 1 additional serving/day was 1.00 (95% CI = 0.96–1.04) among women and 1.05 (95% CI = 0.99–1.11) among men. We, therefore, present covariate-adjusted results from each study and from both combined for fruit and vegetable groups in Table 2 for colon cancer and in Table 3 for rectal cancer.

Further subdivision of very low consumption of fruit and vegetables below 1 serving/day similarly did not reveal an elevated colorectal cancer risk. The covariate-adjusted RR of colon cancer for women who reported consuming 3 servings of fruits per week or fewer was 1.34 (95% CI = 0.79–2.27) compared with women consuming 5 or more servings/day and 0.84 (95% CI = 0.26–2.71) for women who reported consuming 3 servings of vegetables per week or fewer. The respective values among men were 0.36 (95% CI = 0.16–0.82) for fruit (but this estimate was based on eight cases of colon cancer only) and 0.75 (95% CI = 0.29–1.92) for vegetable consumption.

No important associations or trends emerged in the fruit and vegetable subgroups, such as citrus fruit, fruits and vegetables rich in vitamin C, green leafy vegetables, cruciferous vegetables, and potatoes. The only exception was legumes; consumption of 1 additional serving of legumes per day was associated with an RR for colon cancer of 1.49 (95% CI = 1.04–2.12) among women and 0.90 (95% CI = 0.57–1.42) among men (Table 2). For rectal cancer, the corresponding RR estimates were 1.46 (95% CI = 0.72–2.99) among women and 1.55 (95% CI = 0.91–2.63) among men (Table 3).

The null relation between fruit and vegetable consumption and colon cancer incidence was consistent across strata of vitamin supplement use and smoking status (Table 4). Similarly, no association was found among women or men who never smoked and never took vitamin supplements (data not shown). We also examined the association among women and men who either reported a family history of colorectal cancer, had a sigmoidoscopy or colonoscopy, or had a polyp detected. Results did not differ for fruit or vegetable intake (data not shown). Similarly, when the analysis was restricted to women or men without any of these risk factors, results did not change (data not shown).

Results did not differ materially when only data from the baseline diet questionnaire (1980 for women and 1986 for men) were used (data not shown). Moreover, the findings did not change appreciably when we considered only women who did not change their fruit and vegetable consumption during dietary follow-up, i.e., did not change their intake of fruit and vegetables by more than 2 servings/day between June 1984 and June 1986 and between June 1986 and June 1990 (data not shown). Exclusion of participants who regularly consumed breakfast cereal fortified with folate did not affect the overall results (data not shown). The relation between fruit and vegetable consumption and colon and rectal cancer risk also remained null across different strata of alcohol consumption or BMI (data not shown).

Intake of individual fruits and vegetables that constitute the composite items was not appreciably associated with colon or rectal cancer risk in women or men. The only exception was prune consumption; the RR of colon cancer associated with a 1-serving-per-day higher prune consumption was 1.46 (95% CI = 0.93–2.31) among women and 1.73 (95% CI = 1.20–2.50) among men.

Discussion

In these two longitudinal studies of women and men with repeated diet assessment over time, we found no overall association between fruit and vegetable consumption and colon or rectal cancer incidence. Furthermore, we did not find evidence of any appreciable benefit from any of the specific subgroups of

Table 2. Cumulative updated fruit and vegetable consumption and subsequent relative risk of colon cancer among women in the Nurses' Health Study and men in the Health Professionals' Follow-up Study*

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	2 servings/day or fewer	3 servings/day	4 servings/day	5 servings/day	≥6 servings/day	
All fruits and vegetables						
RR, women‡	1.0 (referent)	0.95	0.87	1.06	0.96	1.00 (0.96–1.04)
RR, men§	1.0 (referent)	1.22	1.25	1.09	1.28	1.05 (0.99–1.11)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.09 (0.86–1.37)	1.05 (0.83–1.32)	1.07 (0.83–1.38)	1.08 (0.84–1.38)	1.02 (0.98–1.05)
Total No. of cases	129	172	177	161	298	937
Total person-years of follow-up	273 734	322 059	341 715	285 749	520 388	1 743 645

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/day or fewer	2 servings/day	3 servings/day	4 servings/day	≥5 servings/day	
All fruit						
RR, women‡	1.0 (referent)	0.85	0.81	0.90	0.80	0.96 (0.89–1.03)
RR, men§	1.0 (referent)	1.28	1.31	1.29	1.35	1.08 (1.00–1.16)
RR, pooled (95% CI, pooled)	1.0 (referent)	‖	‖	‖	‖	‖
Total No. of cases	261	308	207	96	65	
Total person-years of follow-up	562 443	571 353	359 309	147 904	102 636	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/day or fewer	2 servings/day	3 servings/day	4 servings/day	≥5 servings/day	
All vegetables						
RR, women‡	1.0 (referent)	0.87	1.11	1.09	0.96	1.03 (0.97–1.10)
RR, men§	1.0 (referent)	0.92	1.11	1.05	1.24	1.01 (0.90–1.14)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.90 (0.75–1.08)	1.11 (0.90–1.38)	1.08 (0.82–1.43)	1.00 (0.72–1.38)	1.03 (0.97–1.09)
Total No. of cases	301	249	207	106	74	
Total person-years of follow-up	512 886	538 301	365 852	187 137	139 469	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/wk or fewer	2–4 servings/wk	5–6 servings/wk	1 serving/day	≥2 servings/day	
Total citrus fruit						
RR, women‡	1.0 (referent)	1.07	0.93	0.81	0.97	0.93 (0.82–1.05)
RR, men§	1.0 (referent)	1.09	1.07	1.31	1.19	1.09 (0.96–1.23)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.08 (0.86–1.34)	0.98 (0.77–1.25)	‖	1.05 (0.80–1.39)	1.00 (0.92–1.09)
Total No. of cases	133	208	137	370	89	
Total person-years of follow-up	274 369	388 947	262 361	669 409	148 559	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/wk or fewer	2–4 servings/wk	5–6 servings/wk	1 serving/day	≥2 servings/day	
Fruits and vegetables rich in vitamin C						
RR, women‡	1.0 (referent)	0.85	0.72	0.77	0.78	0.93 (0.83–1.04)
RR, men§	1.0 (referent)	1.02	0.70	1.16	1.18	1.10 (0.99–1.21)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.90 (0.63–1.29)	0.71 (0.49–1.05)	0.86 (0.63–1.17)	0.88 (0.62–1.24)	‖
Total No. of cases	108	107	76	435	211	
Total person-years of follow-up	323 685	196 461	172 077	738 655	312 767	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/wk or fewer	2 servings/wk	3–4 servings/wk	5–6 servings/wk	≥1 serving/day	
Green leafy vegetables						
RR, women‡	1.0 (referent)	1.15	1.13	1.10	1.02	0.97 (0.81–1.17)
RR, men§	1.0 (referent)	1.34	1.05	1.32	1.23	1.01 (0.84–1.22)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.22 (0.94–1.57)	1.10 (0.90–1.35)	1.18 (0.95–1.47)	1.10 (0.88–1.37)	0.99 (0.87–1.13)
Total No. of cases	176	106	243	203	209	
Total person-years of follow-up	441 381	172 406	460 649	322 694	346 514	

(Table continues)

Table 2 (continued). Cumulative updated fruit and vegetable consumption and subsequent relative risk of colon cancer among women in the Nurses' Health Study and men in the Health Professionals' Follow-up Study*

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	<1 serving/wk	1 serving/wk	2 servings/wk	3–4 servings/wk	⩾5 servings/wk	
Cruciferous vegetables						
RR, women‡	1.0 (referent)	0.93	0.95	1.06	0.94	1.08 (0.83–1.41)
RR, men§	1.0 (referent)	0.98	0.77	0.78	0.83	0.92 (0.70–1.20)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.95 (0.74–1.23)	0.87 (0.68–1.12)	0.92 (0.72–1.18)	0.89 (0.68–1.15)	1.00 (0.83–1.21)
Total No. of cases	87	183	222	263	182	
Total person-years of follow-up	164 454	388 867	452 606	442 968	294 748	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	<1 serving/wk	1–2 servings/wk	3 servings/wk	4 servings/wk	⩾5 servings/wk	
Potatoes						
RR, women‡	1.0 (referent)	1.00	1.02	1.09	1.12	0.94 (0.72–1.23)
RR, men§	1.0 (referent)	0.96	1.36	1.22	1.07	0.92 (0.67–1.28)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.98 (0.74–1.31)	1.10 (0.87–1.39)	1.12 (0.88–1.44)	1.11 (0.86–1.43)	0.93 (0.76–1.15)
Total No. of cases	108	99	269	223	238	
Total person-years of follow-up	228 590	181 178	470 023	404 245	459 609	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	<1 serving/wk	1 serving/wk	2 servings/wk	3 servings/wk	⩾4 servings/wk	
Legumes						
RR, women‡	1.0 (referent)	1.19	1.25	1.25	1.28	1.49 (1.04–2.12)
RR, men§	1.0 (referent)	1.14	0.88	1.02	0.97	0.90 (0.57–1.42)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.17 (0.96–1.42)	1.11 (0.90–1.35)	1.15 (0.95–1.40)	1.12 (0.89–1.42)	1.23 (0.93–1.63)
Total No. of cases	210	188	185	230	124	
Total person-years of follow-up	453 819	349 998	350 406	385 104	204 318	

*RR = relative risk; CI = confidence interval.

†RR estimates for 1 additional serving/day were obtained by calculation of the daily intake from the frequencies prespecified on the food-frequency questionnaire and the use of the resulting variable as a continuous variable.

‡RR and 95% CI estimates adjusted for age, family history of colorectal cancer, sigmoidoscopy, height, body mass index, pack-years of smoking, alcohol intake, physical activity, menopausal status, postmenopausal hormone use, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption.

§RR and 95% CI estimates adjusted for age, family history of colorectal cancer, sigmoidoscopy, height, body mass index, pack-years of smoking, alcohol intake, physical activity, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption.

‖Data were not combined because of statistically significant heterogeneity (at *P*<.05) in RR estimates from women and men.

fruits and vegetables considered, including citrus fruit, fruits and vegetables rich in vitamin C, green leafy vegetables, cruciferous vegetables, potatoes, and legumes.

The association of fruit and vegetable intake with colon and/or rectal cancer incidence has been considered in numerous previous epidemiologic studies, and many of these studies have concluded that strong evidence exists for a benefit [reviewed in *(6)*]. We identified 22 retrospective case–control studies that evaluated the association of vegetable and fruit consumption with colon cancer risk [reviewed in *(6); (20)*]. Of these studies, 18 found some degree of risk reduction with higher level consumption of at least one category of vegetable or fruit. A decreased risk with higher level consumption of cruciferous vegetables was seen in eight of 13 studies in which such an association was reported, and a protective association with intake of green vegetables was reported in five of six studies. In contrast, in a hospital-based case–control study conducted in Japan *(21),* a higher level of fruit and vegetable consumption was associated with an increased risk of colon cancer. Fewer data are available on the association between fruit consumption alone and colon cancer risk; most case–control studies have found no substantial association with risk of colon cancer.

The relation of fruit and vegetable intake to rectal cancer risk was considered in fewer studies. Of 13 case–control studies, eight reported a protective association for at least one fruit or vegetable group [reviewed in *(6)*]. Results have been most consistent for cruciferous vegetables.

The association of fruit and vegetable consumption with colon or rectal cancer incidence was examined prospectively in five studies. In a cohort of Seventh-day Adventists *(22),* no overall association between green salad consumption and colorectal cancer mortality was observed. In a recent incidence analysis from the same cohort *(23),* higher consumption of cooked green vegetables or of salad was not associated with a statistically significant protection from colon cancer, but consumption of legumes more than twice a week was associated with a reduced RR of colon cancer of 0.53 (95% CI = 0.33–0.86) relative to individuals who reported consuming legumes less than once a week or never. In the American Cancer Society's large Cancer Prevention Study II *(24),* colon cancer mortality was reduced in women (RR = 0.62; 95% CI = 0.45–0.86) and men (RR = 0.76; 95% CI = 0.57–1.02) in the highest quintile for vegetable, citrus fruit, and high-fiber grain consumption relative to the lowest quintile. In the Leisure World Study *(25)* of a cohort of elderly Americans residing in California, an inverse association existed only for high-level intake of fruit (3.7

Table 3. Cumulative updated fruit and vegetable consumption and subsequent relative risk of rectal cancer among women in the Nurses' Health Study and men in the Health Professionals' Follow-up Study*

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	2 servings/day or fewer	3 servings/day	4 servings/day	5 servings/day	≥6 servings/day	
All fruits and vegetables						
RR, women‡	1.0 (referent)	0.75	0.87	0.48	0.88	1.00 (0.92–1.09)
RR, men§	1.0 (referent)	1.02	1.12	1.08	1.20	1.06 (0.95–1.18)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.86 (0.55–1.35)	0.97 (0.62–1.50)	0.68 (0.41–1.14)	0.99 (0.62–1.56)	1.02 (0.95–1.09)
Total No. of cases	37	41	51	30	85	244
Total person-years of follow-up	273 734	322 059	341 715	285 749	520 388	1 743 645

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/day or fewer	2 servings/day	3 servings/day	4 servings/day	≥5 servings/day	
All fruit						
RR, women‡	1.0 (referent)	0.64	0.82	0.79	0.66	0.96 (0.83–1.11)
RR, men§	1.0 (referent)	1.30	1.27	0.25	2.04	1.09 (0.94–1.26)
RR, pooled (95% CI, pooled)	1.0 (referent)	‖	0.95 (0.65–1.37)	0.66 (0.37–1.18)	‖	1.02 (0.92–1.13)
Total No. of cases	76	73	57	16	22	
Total person-years of follow-up	562 443	571 353	359 309	147 904	102 636	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/day or fewer	2 servings/day	3 servings/day	4 servings/day	≥5 servings/day	
All vegetables						
RR, women‡	1.0 (referent)	0.86	1.15	1.21	1.24	1.03 (0.91–1.17)
RR, men§	1.0 (referent)	0.81	1.30	1.35	0.67	1.01 (0.80–1.27)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.83 (0.58–1.20)	1.21 (0.80–1.82)	1.24 (0.73–2.09)	1.17 (0.63–2.18)	1.02 (0.92–1.14)
Total No. of cases	74	61	57	30	22	
Total person-years of follow-up	512 886	538 301	365 852	187 137	139 469	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/wk or fewer	2–4 servings/wk	5–6 servings/wk	1 serving/day	≥2 servings/day	
Total citrus fruit						
RR, women‡	1.0 (referent)	0.55	0.79	0.73	0.72	0.98 (0.78–1.23)
RR, men§	1.0 (referent)	1.22	0.89	0.92	1.50	1.12 (0.89–1.40)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.75 (0.49–1.14)	0.82 (0.52–1.29)	0.79 (0.54–1.15)	0.97 (0.58–1.64)	1.05 (0.89–1.23)
Total No. of cases	42	46	37	94	25	
Total person-years of follow-up	274 369	388 947	262 361	669 409	148 559	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/wk or fewer	2–4 servings/wk	5–6 servings/wk	1 serving/day	≥2 servings/day	
Fruits and vegetables rich in vitamin C						
RR, women‡	1.0 (referent)	1.16	0.52	0.83	0.63	0.85 (0.68–1.07)
RR, men§	1.0 (referent)	2.81	2.51	2.87	2.52	1.11 (0.91–1.34)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.30 (0.62–2.73)	0.68 (0.29–1.58)	0.95 (0.49–1.84)	0.76 (0.36–1.61)	0.99 (0.86–1.15)
Total No. of cases	27	35	19	117	46	
Total person-years of follow-up	323 685	196 461	172 077	738 655	312 767	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	1 serving/wk or fewer	2 servings/wk	3–4 servings/wk	5–6 servings/wk	≥1 servings/day	
Green leafy vegetables						
RR, women‡	1.0 (referent)	0.95	0.76	0.81	0.93	0.91 (0.62–1.33)
RR, men§	1.0 (referent)	1.03	0.52	0.46	0.65	0.71 (0.46–1.12)
RR, pooled (95% CI, pooled)	1.0 (referent)	0.98 (0.62–1.54)	0.67 (0.45–0.99)	0.67 (0.44–1.02)	0.80 (0.54–1.19)	0.82 (0.62–1.10)
Total No. of cases	59	32	54	42	57	
Total person-years of follow-up	441 381	172 406	460 649	322 694	346 514	

(Table continues)

Table 3 (continued). Cumulative updated fruit and vegetable consumption and subsequent relative risk of rectal cancer among women in the Nurses' Health Study and men in the Health Professionals' Follow-up Study*

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	<1 serving/wk	1 serving/wk	2 servings/wk	3–4 servings/wk	⩾5 servings/wk	
Cruciferous vegetables						
RR, women‡	1.0 (referent)	1.56	1.33	1.42	1.74	1.19 (0.72–1.95)
RR, men§	1.0 (referent)	1.21	0.66	1.08	0.91	0.97 (0.58–1.62)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.40 (0.80–2.42)	1.00 (0.57–1.76)	1.25 (0.73–2.15)	1.29 (0.74–2.26)	1.08 (0.75–1.54)
Total No. of cases	17	53	52	70	52	
Total person-years of follow-up	164 454	388 867	452 606	442 968	294 748	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	<1 serving/wk	1–2 servings/wk	3 servings/wk	4 servings/wk	⩾5 servings/wk	
Potatoes						
RR, women‡	1.0 (referent)	1.63	1.05	1.28	1.03	0.85 (0.49–1.48)
RR, men§	1.0 (referent)	1.92	1.50	1.02	1.83	1.05 (0.58–1.89)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.69 (0.99–2.90)	1.13 (0.69–1.83)	1.22 (0.74–2.02)	1.18 (0.69–2.00)	0.94 (0.63–1.41)
Total No. of cases	25	37	64	54	64	
Total person-years of follow-up	228 590	181 178	470 023	404 245	459 609	

	Frequencies of intake					RR (95% CI) for 1 additional serving/day†
	<1 serving/wk	1 serving/wk	2 servings/wk	3 servings/wk	⩾4 servings/wk	
Legumes						
RR, women‡	1.0 (referent)	0.99	1.11	1.21	1.14	1.46 (0.72–2.99)
RR, men§	1.0 (referent)	1.91	0.93	0.76	1.72	1.55 (0.91–2.63)
RR, pooled (95% CI, pooled)	1.0 (referent)	1.27 (0.86–1.88)	1.06 (0.71–1.57)	1.06 (0.72–1.57)	1.38 (0.87–2.18)	1.52 (0.99–2.32)
Total No. of cases	54	51	46	54	39	
Total person-years of follow-up	453 819	349 998	350 406	385 104	204 318	

*RR = relative risk; CI = confidence interval.

†RR estimates for 1 additional serving/day were obtained by calculation of the daily intake from the frequencies prespecified on the food-frequency questionnaire and the use of the resulting variable as a continuous variable.

‡RR and 95% CI estimates adjusted for age, family history of colorectal cancer, sigmoidoscopy, height, body mass index, pack-years of smoking, alcohol intake, physical activity, menopausal status, postmenopausal hormone use, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption.

§RR and 95% CI estimates adjusted for age, family history of colorectal cancer, sigmoidoscopy, height, body mass index, pack-years of smoking, alcohol intake, physical activity, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption.

‖Data were not combined because of statistically significant heterogeneity (at $P<.05$) in RR estimates from women and men.

servings/day or more) among women (RR = 0.50; 95% CI = 0.31–0.80) but not among men (RR = 1.12; 95% CI = 0.69–1.81), and no significant association was seen for vegetable consumption in either sex (women: RR = 0.72; 95% CI = 0.45–1.16; men: RR = 1.39; 95% CI = 0.84–2.30). Among men, vegetable consumption, especially high intake of dark green vegetables (0.3 serving/day or more versus <0.11 serving/day), was associated with an elevated incidence of colon cancer (RR = 2.28; 95% CI = 1.33–3.91) *(25).* In the Iowa Women's Health Study *(26),* vegetable intake of more than 4 servings/day compared with fewer than 2 servings/day was associated with an RR of colon cancer of 0.73 (95% CI = 0.47–1.13); fruit consumption of more than 2 servings/day (compared with fewer than 1 serving/day) had an RR of 0.86 (95% CI = 0.58–1.29). In the Netherlands Cohort Study *(27),* an inverse association was found for the highest quintile of combined fruit and vegetable intake and colon cancer risk among women (RR = 0.66; 95% CI = 0.44–1.01) but not among men. No important associations were found for rectal cancer *(27).*

Although in most previous studies multiple fruits and vegetables or groups of these foods were considered, often only one food or food group emerged as inversely related to colon or rectal cancer incidence. In the Iowa Women's Health Study *(26),* only garlic consumption was found to be inversely associated with colon cancer risk. In an Australian case–control study *(28),* only consumption of legumes was inversely related to colon cancer risk. Because such studies in which only one or two food groups were found to be protective were usually considered to be "positive" studies, the overall protective effect of fruits and vegetables on colorectal cancer has probably been overstated.

Fruit and vegetable consumption has been associated more often with a reduced colorectal cancer risk in case–control studies than in prospective cohort studies. Because diet is assessed after the diagnosis of cancer in case–control studies, recall bias may account for the differences between case–control and cohort studies, since healthy control subjects may be more likely to overestimate their fruit and vegetable consumption or cancer patients may underreport it. Another potential bias affecting case–control studies is selection bias. Study participation is usually high for case patients but lower for control subjects; those who participate are likely to be more health-conscious and, thus, to consume more fruits and vegetables. It is possible that the methods used to measure diet in the case–control studies, which typically involve a professional interview rather than a self-administered questionnaire, are more accurate. This was addressed in a study by Jain et al. *(29),* who used our FFQ and their

Table 4. Cumulative updated fruit and vegetable consumption and subsequent relative risk of colon cancer for 1 additional serving/day among women in the Nurses' Health Study and men in the Health Professionals' Follow-up Study, stratified by vitamin supplement use and smoking

	No vitamin supplement		Vitamin supplement	
No. of cases among women	207		362	
No. of cases among men	109		259	
Total No. of cases	316		621	
	RR*	95% CI*	RR*	95% CI*
All fruits and vegetables	0.99	0.93–1.06	1.03	0.99–1.07
All fruit	0.97	0.88–1.07	1.04	0.98–1.11
All vegetables	1.02	0.92–1.13	1.03	0.97–1.11
Total citrus fruit	0.97	0.83–1.13	1.02	0.92–1.13
Fruits and vegetables rich in vitamin C	1.00	0.88–1.15	1.04	0.95–1.13
Green leafy vegetables	0.98	0.77–1.25	1.00	0.85–1.17
Cruciferous vegetables	0.94	0.66–1.34	1.04	0.83–1.30
Potatoes	0.82	0.55–1.24	0.96	0.72–1.29
Legumes	1.52	0.91–2.54	Women: 1.55†	1.04–2.31†
			Men: 0.65†	0.37–1.16†

	Never smokers‡		Ever smokers‡	
No. of cases among women	248		244	
No. of cases among men	93		235	
Total No. of cases	341		479	
	RR*	95% CI*	RR*	95% CI*
All fruits and vegetables	1.00	0.95–1.06	1.02	0.97–1.07
All fruit	0.99	0.91–1.07	Women: 0.94†	0.84–1.05†
			Men: 1.10†	1.00–1.21†
All vegetables	1.02	0.94–1.12	1.03	0.95–1.11
Total citrus fruit	1.01	0.88–1.16	1.01	0.90–1.14
Fruits and vegetables rich in vitamin C	0.98	0.87–1.11	1.06	0.96–1.17
Green leafy vegetables	1.07	0.87–1.31	0.93	0.77–1.12
Cruciferous vegetables	1.06	0.79–1.42	0.95	0.73–1.25
Potatoes	0.75	0.49–1.13	1.09	0.80–1.47
Legumes	0.98	0.60–1.62	1.34	0.93–1.95

*Relative risk (RR) and 95% confidence interval (CI) estimates were adjusted for age, family history of colorectal cancer, sigmoidoscopy, height, body mass index, pack-years of smoking, alcohol intake, physical activity, aspirin use, vitamin supplement intake, total caloric intake, and red meat consumption and, among women, additionally for menopausal status and postmenopausal hormone use.

†Data are presented separately for women and men because of statistically significant heterogeneity (at P<.05) in RR estimates from women and men.

‡Analysis stratified by smoking history was restricted to individuals for whom information on smoking was available.

state-of-the-art diet history conducted by interview. In comparison with diet records collected from the same person, the FFQ performed at least as well as the interviewer method. Furthermore, the repeated administrations of the FFQ in our study further enhance the precision of dietary assessments *(10).* Although the consumption of fruit and vegetables may be overreported, relative consumption is reported reasonably well compared with detailed weighing and recording of intake *(14).* Thus, any important association should have been detected, although a weak relation cannot be excluded. Reported total caloric intake, which was not an important predictor of colorectal cancer in either of our cohorts, was associated with higher fruit and vegetable consumption (Table 1). This finding, in part, reflects higher consumption of all foods by larger or more active persons, but it could also reflect overreporting and underreporting and underlines the importance of adjusting for energy intake.

The assessment of diet is inevitably affected by measurement error. The NHS and the HPFS are the only cohorts in which repeated assessments of diet are available. The use of cumulatively updated dietary data reduces random (but not systematic) within-person measurement error [chapter 6 in *(10)*]. Methods to correct for measurement error of repeatedly assessed and averaged dietary data have not yet been developed but may have improved the validity of the results.

Frequent consumption of fruit and vegetables is associated with a number of predictors of colorectal cancer, such as high physical activity, high vitamin supplement use, low alcohol consumption, and low cigarette smoking *(30),* and high fruit consumption tends to be accompanied by lower intake of red meat. Confounding by measured and unmeasured factors is of considerable concern in studies of diet and disease. Many of these potential confounders for colorectal cancer had not been appreciated or measured until recently; thus, some of the previous studies that found an apparent protective effect of high intake of fruit and vegetables may have been confounded by other lifestyle factors. While we did not find any of the potential confounders that we considered in our adjusted analyses to appreciably alter our estimates, the degree of confounding might be greater in populations that are more heterogeneous in education and occupation than the populations in the NHS and HPFS. Residual confounding, e.g., by meat intake, due to measurement error has to be considered in our cohorts. However, to the extent that residual confounding exists because of health-conscious behavior, this would tend to overstate a protective effect of fruit and vegetable intake.

Our finding of an elevated RR of colon cancer associated with prune consumption was unexpected and merits examination in other studies. This association might be the result of reverse causality—a high prune consumption might result from symptoms of constipation secondary to neoplasia. However, neither constipation nor laxative use was associated with colon cancer incidence in the NHS *(31)*.

If diet plays an important role in colorectal carcinogenesis, it may well be in the more distant past (even decades earlier, e.g., during adolescence or even preschool age). Findings from our cohorts suggest that folate is particularly important 15 or more years before diagnosis *(4)*. When examining fruit and vegetable consumption in relation to the incidence of adenomas, we also found no association *(32)*, suggesting that our null results were not simply due to inadequate follow-up time. The NHS spans 16 years of follow-up since the first diet assessment, and the availability of repeated dietary measures permits a consideration of both distant and more proximate dietary intake. Analyses using only baseline dietary information did not alter our overall findings, also reducing the likelihood that we missed an effect because of insufficient follow-up, but we cannot exclude a beneficial effect that acts decades before diagnosis.

We have recently reported the lack of an association between dietary fiber and risk of colorectal cancer in the NHS *(7)*. Two randomized trials *(33,34)* have failed to show any association between fiber consumption and the recurrence of colorectal adenomas. These reports and our study provide results that challenge widely held beliefs, since colorectal cancer is currently considered the cancer that is most likely modifiable by a "healthy" diet. Specifically, dietary guidelines recommend high intake of fruit, vegetables, and fiber to reduce risk of colorectal cancer *(35,36)*. In fact, systemic factors (e.g., growth factors, in particular insulin and insulin-like growth factors) may be more important than intraluminal factors in promoting tumor growth once cell proliferation has been initiated *(37–39)*.

Finally, our results may depend on sufficient variation in fruit and vegetable consumption. While some of our study participants reported quite low intake, others reported consumption in excess of 5 servings/day (Fig. 1). This does not exclude the possibility of an excess risk of colorectal cancer with very low fruit and vegetable consumption. In our data, however, we did not find an association between very low consumption of fruit and vegetables (3 servings per week or fewer) and colorectal cancer incidence.

Our findings need to be considered in the context of the accumulating evidence that folate may confer protection against colorectal cancer. In many populations consuming diets composed largely of minimally processed foods and little or no use of supplementation or fortification, fruits and vegetables are the major source of folate. In the NHS and HPFS cohorts, as well as in many segments of the current U.S. population, the important sources of folate include multivitamin supplements, fortified breakfast cereals, and orange juice. More recently, fortified grains have become a major source of folate. Because of these additional sources of folate, fruits and vegetables may no longer be the major determinants of folate status. Indeed, in subsamples of the NHS and HPFS, folate intake from all sources, including multivitamins, correlated well with erythrocyte folate level, but the correlation between folate level and fruit (Pearson $r = .22$ in the NHS; Pearson $r = .04$ in the HPFS) and vegetable intake (Pearson $r = .12$ in the NHS; Pearson $r = .12$ in the HPFS) was low. Our current results do not exclude the possibility that, in populations for which fruits and vegetables are important determinants of folate status, these may be associated with lower risk of colorectal cancer.

In conclusion, high consumption of fruit and vegetables did not appear to be protective against cancers of the colon and rectum in our large U.S. cohorts. A diet rich in these foods remains advisable, however, because it conveys protection against other diseases, such as cardiovascular disease *(40)* and possibly other cancers *(6,41)*.

Appendix Table 1. Definition of fruit and vegetable groups in the Nurses' Health Study

Food groups	1980	1984	1986	1990
All fruit	Apples Apricots Bananas Oranges Peaches Pears Plums Other fruit (fresh or canned) Grapefruit juice Orange juice	Apples Apricots Bananas Blueberries Cantaloupe Grapefruit Grapes Oranges Peaches Pears Plums Prunes Raisins Strawberries Watermelon Apple cider Apple juice Grapefruit juice Orange juice Other fruit juices	Apples Applesauce Apricots Avocado Bananas Blueberries Cantaloupe Fruit cocktail Grapefruit Grapes Oranges Other canned fruit Peaches Pears Plums Prunes Raisins Strawberries Watermelon Apple cider Apple juice Grapefruit juice Orange juice Other fruit juices	Apples Applesauce Apricots Bananas Blueberries Cantaloupe Grapefruit Grapes Oranges Peaches Pears Plums Prunes Raisins Strawberries Watermelon Apple cider Apple juice Grapefruit juice Orange juice Other fruit juices

(Appendix table continues)

Appendix Table 1 (continued). Definition of fruit and vegetable groups in the Nurses' Health Study

Food groups	1980	1984	1986	1990
All vegetables	Broccoli Brussels sprouts Cabbage Carrots Cauliflower Corn Lima beans Peas Spinach or other greens String beans Sweet potatoes Tomatoes Tomato juice Yellow squash	Alfalfa sprouts Beets Broccoli Brussels sprouts Cabbage Carrots Cauliflower Celery Chard greens Coleslaw Corn Eggplant Garlic Head lettuce Iceberg lettuce Kale Leaf lettuce Lima beans Mixed vegetables Mushrooms Mustard greens Peas Romaine lettuce Soybeans Spinach String beans Summer squash Sweet potatoes Tofu Tomatoes Yams Yellow squash Zucchini	Alfalfa sprouts Broccoli Brussels sprouts Cabbage Carrots Cauliflower Celery Chard greens Coleslaw Corn Cucumber Eggplant Green pepper Head lettuce Iceberg lettuce Kale Leaf lettuce Mixed vegetables Mushrooms Mustard greens Peas Red chili sauce Romaine lettuce Sauerkraut Soybeans Spinach String beans Summer squash Sweet potatoes Tofu Tomato juice Tomato sauce Tomatoes Winter squash Yams Zucchini	Beets Broccoli Brussels sprouts Cabbage Carrots Cauliflower Celery Chard greens Coleslaw Corn Eggplant Head lettuce Iceberg lettuce Kale Leaf lettuce Lima beans Mixed vegetables Mustard greens Onions Peas Red chili sauce Romaine lettuce Soybeans Spinach String beans Summer squash Sweet potatoes Tofu Tomatoes Tomato juice Tomato sauce Winter squash Yams Zucchini
All fruits and vegetables	All foods listed in the first 2 categories	All foods listed in the first 2 categories	All foods listed in the first 2 categories	All foods listed in the first 2 categories
Citrus fruit	Oranges Grapefruit juice Orange juice	Grapefruit Oranges Grapefruit juice Orange juice	Grapefruit Oranges Grapefruit juice Orange juice	Grapefruit Oranges Grapefruit juice Orange juice
Fruits and vegetables rich in vitamin C	Broccoli Oranges Grapefruit juice Orange juice	Broccoli Brussels sprouts Cantaloupe Grapefruit Oranges Strawberries Grapefruit juice Orange juice Other fruit juices	Broccoli Brussels sprouts Cantaloupe Grapefruit Green peppers Oranges Strawberries Grapefruit juice Orange juice Other fruit juices	Broccoli Brussels sprouts Cantaloupe Grapefruit Oranges Strawberries Grapefruit juice Orange juice Other fruit juices
Green leafy vegetables	Spinach or other greens	Chard greens Head lettuce Iceberg lettuce Kale Leaf lettuce Mustard greens Romaine lettuce Spinach	Chard greens Head lettuce Iceberg lettuce Kale Leaf lettuce Mustard greens Romaine lettuce Spinach	Chard greens Head lettuce Iceberg lettuce Kale Leaf lettuce Mustard greens Romaine lettuce Spinach
Cruciferous vegetables	Broccoli Brussels sprouts Cabbage Cauliflower	Broccoli Brussels sprouts Cabbage Cauliflower Coleslaw Kale	Broccoli Brussels sprouts Cabbage Cauliflower Coleslaw Kale Sauerkraut	Broccoli Brussels sprouts Cabbage Cauliflower Coleslaw Kale
Potatoes	Potatoes (mashed or baked) French fries Potato chips	Potatoes (mashed or baked) French fries Potato chips	Potatoes (mashed or baked) French fries Potato chips	Potatoes (mashed or baked) French fries Potato chips
Legumes	Beans Lentils Lima beans Peas	Beans Lentils Lima beans Peas Soybeans Tofu	Beans Lentils Lima beans Peas Soybeans Tofu	Beans Lentils Lima beans Peas Soybeans Tofu

Appendix Table 2. Definition of fruit and vegetable groups in Health Professionals' Follow-up Study

Food groups	1986	1990
All fruit	Apples Apricots Avocado Bananas Blueberries Cantaloupe Grapefruit Oranges Peaches Pears Plums Raisins Strawberries Watermelon Apple cider Apple juice Grapefruit juice Orange juice Other fruit juices	Apples Applesauce Apricots Bananas Blueberries Cantaloupe Grapefruit Oranges Peaches Pears Plums Prunes Raisins Strawberries Watermelon Apple cider Apple juice Grapefruit juice Orange juice Other fruit juices
All vegetables	Alfalfa sprouts Broccoli Brussels sprouts Cabbage Carrots Cauliflower Celery Chard greens Coleslaw Corn Eggplant Garlic Green pepper Head lettuce Iceberg lettuce Kale Leaf lettuce Lima beans Mixed vegetables Mushrooms Mustard greens Peas Red chili sauce Romaine lettuce Sauerkraut Soybeans Spinach String beans Summer squash Sweet potatoes Tofu Tomato juice Tomato sauce Tomatoes Winter squash Yams Zucchini	Beets Broccoli Brussels sprouts Cabbage Carrots Cauliflower Celery Chard greens Coleslaw Corn Eggplant Head lettuce Iceberg lettuce Kale Leaf lettuce Lima beans Mixed vegetables Mustard greens Onions Peas Red chili sauce Romaine lettuce Soybeans Spinach String beans Summer squash Sweet potatoes Tofu Tomato juice Tomato sauce Tomatoes Winter squash Yams Zucchini
All fruits and vegetables	All foods listed in the first 2 categories	All foods listed in the first 2 categories
Citrus fruit	Grapefruit Oranges Grapefruit juice Orange juice	Grapefruit Oranges Grapefruit juice Orange juice
Fruits and vegetables rich in vitamin C	Broccoli Brussels sprouts Cantaloupe Grapefruit Green peppers Orange Strawberries Grapefruit juice Orange juice Other fruit juices	Broccoli Brussels sprouts Cantaloupe Grapefruit Oranges Strawberries Grapefruit juice Orange juice Other fruit juice
Green leafy vegetables	Chard greens Head lettuce Iceberg lettuce Kale Leaf lettuce Mustard greens Romaine lettuce Spinach	Chard greens Head lettuce Iceberg lettuce Kale Leaf lettuce Mustard greens Romaine lettuce Spinach
Cruciferous vegetables	Broccoli Brussels sprouts Cabbage Cauliflower Coleslaw Kale Sauerkraut	Broccoli Brussels sprouts Cabbage Cauliflower Coleslaw Kale
Potatoes	Potatoes (mashed or baked) French fries Potato chips	Potatoes (mashed or baked) French fries Potato chips
Legumes	Beans Lentils Lima beans Peas Soybean Tofu	Beans Lentils Lima beans Peas Soybeans Tofu

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NOTES

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